

## Summary of Change

### AR 40-7

#### Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Substances

This revision –

- ❑ Specifies the requirement to apply the same standard for Department of the Army sponsored research conducted outside the United States as used with research conducted in the United States with regard to the filing of an investigational new drug application or investigational device exemption with the Food and Drug Administration. (para 1-4)
- ❑ Adds the responsibilities of the Commander, U.S. Army Medical Research and Materiel Command and the Commanders of the Regional Medical Commands. (paras 2-2 and 2-4)
- ❑ Redesignates the Human Use Review and Regulatory Affairs Office as the Office of Regulatory Compliance and Quality. (para 2-1)
- ❑ Redesignates the Clinical Investigation Program Division as the Clinical Investigation Regulatory Office. (para 2-1)
- ❑ Expands on responsibilities of investigators to include the requirement to document completion of Good Clinical Practice training within twelve months of the initial review of the protocol by the IRB of record and to submit financial disclosure statements to sponsors as required by 21 CFR 54. (para 2-9)
- ❑ Adds the responsibilities of the medical monitor. (para 2-9)
- ❑ Identifies essential elements of information for investigators to include in continuing review reports. (para 2-9)
- ❑ Requires that final reports be submitted in one of the standard forms in the International Conference of Harmonization Guideline for Industry: Structure and Content of Clinical Study Reports (E3). (para 2-9)
- ❑ Requires that research or clinical investigation protocols that use investigational drugs or devices be prepared in a format prescribed in the International Conference of Harmonization Guideline for Good Clinical Practice: Consolidated Guideline. (paras 2-9)
- ❑ Identifies the requirement for institutions conducting research with human participants to require that research investigators, IRB members and staff, and other

relevant personnel maintain continuing knowledge of, and comply with relevant policies for the protection of human participants in research. (para 2-9)

- ❑ Includes separate chapter describing: Procedures for use of investigational drugs and devices in U.S. Army Military Treatment Facilities, Dental Treatment Facilities, and Research, Development, Test, and Evaluation Facilities. (chap 4)
- ❑ Identifies procedures for review and approval of protocol amendments. (para 4-7)
- ❑ Identifies requirement for continuing review of research by IRBs. (para 4-9)
- ❑ Includes separate chapter describing: Investigational drug and device use control. (chap 5)
- ❑ Includes separate chapter describing: Special Considerations. Special considerations include: reporting of adverse events with investigational drugs or devices, use of an approved drug for an unapproved indication, emergency procurement of drugs and biologicals from foreign suppliers, and use of Schedule I controlled substances. (chap 6)
- ❑ Changes the time of submission of reports of adverse events. (para 6-1)
- ❑ Adds sponsor responsibilities for reporting serious and unexpected adverse events associated with the use of investigational new drugs to both participating investigators and to the FDA. (para 6-1)
- ❑ Removes information concerning medical device adverse events and relocates this information to a new separate paragraph. (para 6-1 and 6-2, respectively)
- ❑ Deletes information formerly contained in appendix B (Progress Reports for Investigational Drugs and Devices), Appendix C (Investigational New Drug Application Format), and Appendix D (Investigational Device Exemption). These appendices included information that was subject to frequent change by external authorities such as the Food and Drug Administration. The most current requirements for these topics can be found on the World Wide Web; therefore, pertinent references are cited and the applicable web site address (URL) is provided in Appendix A.
- ❑ Includes information on the Control of Investigational Drugs Used to Treat Patients Returning to a Military Treatment Facility from a United States Army Medical Center. (Appendix B). This information was formerly contained in the U.S. Army Health Services Command supplement to AR 40-7.
- ❑ Includes a Management Control Evaluation Checklist. (Appendix C).

- ❑ Includes general information on the regulation of medical devices. (Appendix D)
- ❑ Adds throughout the document, where appropriate, regulatory citations for medical devices.
- ❑ Makes editorial changes throughout the document to consistently define command units and consistently use abbreviations and acronyms.
- ❑ Introduces the term “participant” to replace the reference to human “subjects.” This term is introduced based on recommendations from the April 2001 report of the National Bioethics Advisory Commission entitled, “Ethical and Policy Issues in Research Involving Human Participants.” This report recommends the use of the term “participant” in an effort to use a term that is appropriate and respectful to the individuals who participate in research.

Headquarters  
Regulation 40-7  
Department of the Army  
Washington, DC  
date  
date

\*Army

Effective

## Medical Services

### Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Substances

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By Order of the Secretary of the Army:

ERIC K. SHINSEKI  
General, United States Army  
Chief of Staff

Official:

JOEL B. HUDSON  
Administrative Assistant to the  
Secretary of the Army

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**History.** This printing publishes a revision of this publication. Changes made to this publication since the last revision are not highlighted due to substantial reorganization of the document.

**Summary.** This revision incorporates International Conference on Harmonization guidelines for good clinical practice, adds procedures for the control of investigational drugs used to treat patients returning to military treatment facilities from U.S. Army Medical Centers (MEDCEN), and updates office symbols and addresses used throughout the document. It implements DOD Directive 3216.1, DOD Directive 3216.2 and DOD Directive 6200.2. It also provides the URLs (website addresses) for cited documents and information, as appropriate. This revision deletes previous appendices B, C, and D, and provides URL references to this frequently changing material instead. This revision adds new appendices B, C, and D, as noted in the summary of change.

**Applicability.** This regulation applies to the Active Army, members and organizations of

the Army National Guard of the United States (ARNGUS) including periods when operating in their Army National Guard (ARNG) capacity, and U.S. Army Reserve (USAR). It also applies to all research, development, test and evaluation programs and clinical investigation programs conducted or managed by the Army.

Proponent and exception authority. The proponent agency of this regulation is The Surgeon General. The proponent has the authority to approve exceptions to this publication that are consistent with controlling law and regulation. The proponent may delegate this approval authority, in writing, to an individual within the proponent agency in the grade of colonel or the civilian grade equivalent.

Army management control process. This regulation is subject to the requirements of AR 11-2 (Management Control). It contains management control provisions and a checklist for conducting management control evaluations. Appendix C contains the checklist.

Supplementation. Supplementation of this regulation and establishment of command and local forms are prohibited without the prior approval of HQDA (DASG- HSZ), 5109 Leesburg Pike, Falls Church, VA 22041-3258.

Suggested improvements. Users are invited to send comments and suggested improvements on DA Form 2028 (Recommended Changes to Publications and Blank Forms) directly to the Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012.

Distribution. This publication is available in electronic media only (EMO) and is intended for command levels D and E for the Active Army, the Army National Guard, and the U.S. Army Reserve.

\*This regulation supersedes AR 40-7, 4 January 1991.

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## Chapter 1 Introduction

### **1-1. Purpose**

This regulation prescribes Department of the Army (DA) policies, procedures, and responsibilities for the use of investigational new drugs and devices, marketed drugs and devices for unapproved indications in humans, and U.S. Drug Enforcement Administration (DEA) Schedule I controlled substances.

### **1-2. References**

Required and related publications and referenced forms are listed in Appendix A.

### **1-3. Explanation of abbreviations and terms**

Abbreviations and special terms used in this regulation are explained in the Glossary.

### **1-4. Overall principles and guidance**

a. Research with investigational new drugs and devices is of importance to the DA for the following reasons:

(1) The research, development, test, and evaluation (RDT&E) of investigational new drugs and devices designed to treat, prevent, or diagnose diseases that threaten the fighting strength of the soldier are of strategic importance. Because of the unique military nature of many of these items, this research would not be carried out in the private sector.

(2) Clinical investigations of investigational new drugs and devices within Army Military Treatment Facilities (MTF) and Dental Treatment Facilities (DTF) foster the development of new treatment modalities for the benefit of all Defense Enrollment Eligibility Reporting System eligible beneficiaries and potentially the general population. Such clinical investigations are also an integral part of graduate medical education

programs conducted at Army Medical Centers (MEDCEN).

b. Procedures to be followed to ensure protection of the rights and welfare of human participants who participate in investigational new drug or device research will be those described in 32 CFR 219, Department of Defense (DOD) Directive 3216.2, AR 70-25 for RDT&E organizations and AR 40-38 for MTFs and DTFs.

c. Additional protections for human participants in Department of the Army sponsored research conducted outside the United States.

(1) An IND or IDE will be filed whenever research is conducted outside the United States with drugs, vaccines or devices which would require the filing of an IND or IDE if the research were conducted in the United States.

(2) Initial dose ranging, toxicity and safety studies of investigational drugs, vaccines or devices, commonly referred to as Phase I studies, will only be conducted within the United States.

d. Procedures to be followed to ensure humane use of animals in drug and device research are described in DOD Directive 3216.1 and AR 70-18/SECNAVINST 3900.38B/AFR 169-2/DARPAINST 18/DNAINST 3216.1B/USUHINST 3203.

e. An overview of the regulation of medical devices is included in Appendix D.

f. Nothing in this regulation is intended to supersede health hazard or safety reviews required by other Army regulations.

g. Nothing in this regulation allows an investigation to proceed according to the requirements identified in Title 21, part 50.24 of the Code of Federal Regulations (21 CFR 50.24 – Exception from informed consent requirements for emergency research). A change to the requirements identified in 10 USC 980 would be required to proceed

with an investigation in accordance with 21 CFR 50.24.

h. The guidance in this regulation pertains to the following:

(1) Use of investigational new drugs and devices in humans, to include Schedule I controlled substances, in Army MTF, DTF, and RDT&E programs.

(2) Nonclinical use (that is, animal use or *in vitro* testing) of Schedule I controlled substances.

(3) Use of marketed approved drugs and devices for unapproved indications in humans.

i. This regulation does not specifically address the Tri-Service Review Process for HIV Research Protocols. Please refer to the current Memorandum of Agreement among the Surgeons General of the Army, Navy, and Air Force entitled "Consolidated Tri-Service Review Process for Human Immunodeficiency Virus (HIV) Research Protocols Executed Under Cooperative Agreement from the U.S. Army Medical Research and Materiel Command (USAMRMC) to the Henry M. Jackson Foundation for the Advancement of Military Medicine (HMJFAMM)" for current information addressing these protocols. The Memorandum of Agreement can be obtained from the Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012.

j. In this regulation, the term "clinical investigation" refers to clinical investigation as defined in AR 40-38, Clinical Investigation Program.

k. In this regulation, the acronym IRB is used to refer to any institutional review board, ethical review committee, independent ethics review committee, human use committee, or human use review committee.

## Chapter 2

### Responsibilities

#### **2-1. The Surgeon General (TSG)**

TSG will –

- a. Prepare policies and regulations for research using investigational new drugs, devices, or Schedule I controlled substances.
- b. Establish and maintain the Human Subjects Research Review Board (HSRRB).
- c. Establish and maintain, within the Headquarters of U.S. Army Medical Research and Materiel Command (USAMRMC), the Office of Regulatory Compliance and Quality (RCQ) to provide administrative support for TSG's HSRRB.
- d. Be the approving authority for all research protocols involving the use of DA sponsored investigational new drugs or devices.
- e. Be the approving authority for all research protocols conducted with non-DA sponsored and investigator sponsored investigational new drugs and devices in RDT&E facilities.
- f. Be the approving authority for all research protocols involving the use of Schedule I controlled substances conducted or managed by an Army organization.
- g. Acting as the Commander, MEDCOM, establish and maintain within the U.S. Army Medical Department Center & School (AMEDDC&S), the Clinical Investigation Regulatory Office (CIRO) to coordinate, monitor, review and have approval authority for clinical investigations that involve clinical research with non-DA sponsored and investigator-sponsored investigational new drugs or devices within a MTF and DTF.

#### **2-2. The Commander, U.S. Army Medical Research and Materiel Command**

The Commander, USAMRMC will –

- a. Serve as Chairperson of TSG's HSRRB.
- b. Ensure that resources are made available to RCQ to provide adequate administrative support for TSG's HSRRB.
- c. Ensure that quality assurance monitoring of all DA sponsored investigational new drug and device protocols is conducted in accordance with 21 CFR 312.53, 21 CFR 812.46 and the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6), section 5.18.

### **2-3. The Deputy for Regulatory Compliance and Quality, U.S. Army Medical Research and Materiel Command**

The Deputy for Regulatory Compliance and Quality, USAMRMC will—

- a. Serve on behalf of The Surgeon General as sponsor of investigational new drugs and devices.
- b. Submit DA sponsored investigational new drug applications (INDs) and investigational device exemptions (IDEs) to the Food and Drug Administration (FDA).
- c. Submit DA sponsored New Drug Applications (NDAs), Biologics License Applications (BLAs), Premarket Approval Applications (PMA) and Premarket Notifications (510k)s to the FDA.
- d. Prepare and maintain records of all correspondence with the FDA concerning DA sponsored INDs, IDEs, NDAs, BLAs, PMAs and 510(k)s.
- e. Review all information relevant to the safety of a DA sponsored investigational new drug and device and notify FDA and all participating investigators of any investigational new drug adverse experience associated with the use of an

investigational new drug that is both serious and unexpected as defined in 21 CFR 312.32; any adverse effect associated with the use of an investigational device that is unanticipated, as defined by 21 CFR 812.150; and any findings from tests in laboratory animals that suggests a significant risk to human participants.

f. Conduct postmarketing surveillance programs, within the requirements of 21 CFR Parts 314, 601, and 814, for DA sponsored NDAs, BLAs and PMAs.

g. Coordinate the use of DA sponsored investigational products by extramural organizations.

h. Ensure that all requirements of applicable federal regulations, this regulation, AR 40-61, AR 70-25, AR 70-65 and the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use in ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6) are met at sites approved by TSG's HSRRB for research involving investigational new drugs or devices.

i. Ensure protocols reviewed by TSG's HSRRB are in compliance with appropriate human participant protection, environmental, safety, and quality assurance regulatory requirements.

j. Provide quality assurance oversight of DA sponsored IND and IDE investigational new drug and device protocols.

k. Provide administrative support for TSG's HSRRB.

#### **2-4. Commanders of Regional Medical Commands**

When a clinical investigation involving an investigational new drug or device is proposed, the Commanders of the Regional Medical Commands, will—

a. Forward, through CIRO, to the Commander, U.S. Army Medical Research and

Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012 all protocols involving DA sponsored investigational new drugs or devices used within the Regional Medical Command, to include those involving Schedule I controlled substances, regardless of the sponsor.

b. Forward to the Commander, U.S. Army Medical Department Center & School, Clinical Investigation Regulatory Office, ATTN: MCCS-GCI, 1608 Stanley Road, Fort Sam Houston, TX 78234-6125, all protocols involving non-DA sponsored or investigator-sponsored investigational new drugs or devices used within the Regional Medical Command, except those involving Schedule I controlled substances.

c. Ensure that all requirements of applicable federal regulations, this regulation, AR 40-38, AR 40-61, and the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6), are met at sites approved for clinical investigations involving investigational new drugs or devices.

## **2-5. Commander, 18th Medical Command (MEDCOM)**

The Commander, 18th MEDCOM will—

a. Forward to the Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012, all protocols involving investigational new drugs or devices, regardless of sponsor, used within the 18th MEDCOM, to include those involving Schedule I controlled substances.

b. Be the approving authority for emergency procurement and use of investigational new drugs in facilities that are organizationally a part of 18th Medical Command.

c. Ensure that all requirements of applicable federal regulations, AR 40-7, AR 40-

38, AR 40-61, AR 70-25 and the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6), are met at sites approved for clinical investigations involving investigational new drugs or devices.

## **2-6. Commanders of Research, Development, Test, and Evaluation organizations**

Commanders of RDT&E organizations will—

a. Forward to the Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012 for review and approval all protocols involving investigational new drugs or devices conducted or managed within their organization, to include those involving Schedule I controlled substances, regardless of the sponsor.

b. Forward to the respective product manager a copy of the protocol.

c. Ensure investigators within their organization comply with all requirements of applicable federal regulations, this regulation, AR 70-25 and AR 70-65 and the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6).

## **2-7. Organizations with product management responsibility for DA sponsored investigational new drugs and devices**

Organizations with product management responsibility will—

a. Perform duties on behalf of the sponsor for applicable DA sponsored INDs as described in 21 CFR 312.50 through 21 CFR 312.59.

b. Perform duties on behalf of the sponsor for applicable DA sponsored IDEs as described in 21 CFR 812.40 through 21 CFR 812.47.

c. Coordinate resources necessary for maintenance of DA sponsored INDs and IDEs.

- d. Coordinate the preparation of IND and IDE submissions to FDA.
- e. Maintain and update the current investigator brochure as new information

becomes available.

## **2-8. The U.S. Army Medical Department Center and School Clinical Investigation Regulatory Office**

The AMEDDC&S CIRO will—

- a. Review and forward to TSG's HSRRB all research protocols conducted in a MEDCOM MTF or DTF involving:

- (1) DA sponsored investigational new drugs or devices.

- (2) Investigational new drug or device research protocols funded or managed by RDT&E organizations.

- b. Review and approve or disapprove for the Commander, MEDCOM research protocols involving non-DA sponsored investigational new drugs or devices conducted in MEDCOM MTFs and DTFs.

- c. Ensure that all applicable requirements of this regulation, AR 40-38, AR 40-61, AR 70-25 and the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6), are met at sites approved for clinical research of investigational new drugs and devices.

- d. Be the approving authority for emergency procurement and use of investigational new drugs in MEDCOM MTFs and DTFs.

## **2-9. Other responsible parties**

- a. The commercial or non-DA sponsor of an investigational new drug or device will:
  - (1) Prepare and submit an IND or IDE to the FDA.

(2) Maintain records of all correspondence with the FDA concerning INDs or IDEs.

(3) Notify the FDA and all participating investigators of any serious and unexpected adverse events and unanticipated device adverse effects, as defined in 21 CFR 312.32 and 21 CFR 812.3, resulting from the use of the investigational drug or device, respectively.

(4) Perform all other duties of the sponsor of an IND or IDE as detailed in 21 CFR 312.50 through 21 CFR 312.59 or 21 CFR 812.40, respectively.

b. The investigator will:

(1) Prepare a protocol in accordance with the format specified in the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6), section 6, and in accordance with AR 40-38 and AR 70-25.

(2) Obtain IRB approval of the protocol and any amendments before initiation of the investigation and adhere to this approved protocol.

(3) Provide for protection of the rights and welfare of research volunteers in accordance with 21 CFR 50, 32 CFR 219, DoD Directive 3216.2, the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6), section 4.8, and the policies and procedures of AR 40-38 for clinical investigations or AR 70-25 for RDT&E research.

(4) Maintain adequate records of the receipt, storage, use, and disposition of all investigational new drugs, devices and Schedule I controlled substances in accordance with 21 CFR 312.62, 21 CFR 812.140, 21 CFR 312.69 and the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6), section 4.6, and this regulation. In addition, when applicable, military treatment facilities must comply with

AR 40-61 and RDT&E activities must comply with AR 70-65.

(5) Prepare progress reports, final reports, financial disclosure reports and deviation from protocol reports as described under 21 CFR 54, 21 CFR 312.64, 21 CFR 812.150, ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6) and ICH Guideline for Industry: Structure and Content of Clinical Study Reports (E3).

(6) Prepare and submit to IRBs, continuing review reports, which include (a) the number of participants accrued; (b) a description of any adverse events or unanticipated problems involving risks to participants or others and of any withdrawal of participants from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. In conducting continuing review of research, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research.

(7) Report adverse events or unanticipated device adverse effects involving the use of an investigational new drug or device to the sponsor and IRB of record, in accordance with 21 CFR 312.64, 21 CFR 812.150, and the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6), section 4.11. If a DA sponsored IND or IDE, inform the appropriate product manager. In addition, if the protocol was reviewed by TSG's HSRRB, notify the RCQ, USAMRMC of serious and/or unexpected adverse events. Investigators will use protocol-specific case report forms for submitting adverse event reports. If there is not a specific case report form for adverse events, the FDA

Form 3500 (MedWatch) will be used.

(8) Ensure that investigational new drugs or devices are administered to participants only under the principal investigator's (PIs) personal supervision or the personal supervision of a previously approved subinvestigator, in accordance with 21 CFR 312.61, 21 CFR 812.110 and the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6), section 4.6.

(9) Coordinate with the sponsor the preparation of a monitoring plan for all DA sponsored investigational new drug and device protocols to ensure monitoring of the investigational trial as required by 21 CFR 312.56, 21 CFR 812.46 and, ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6), sections 1.38 and 5.18.

(10) Provide documentation of successful completion of a course in the conduct of clinical research in accordance with Good Clinical Practices (GCP) prior to final approval of the protocol for each investigator and sub-investigator identified in the protocol. The GCP course must have been taken within twelve months of the initial review of the protocol by the IRB of record. At the discretion of the IRB during the continuing review process, investigators will also provide annual documentation of completion of one GCP course each year for the duration of the research project.

(11) As required by 21 CFR 54.4, provide the sponsor of the investigational product with sufficient accurate information needed to allow subsequent disclosure or certification of financial arrangements and financial interests with the sponsor.

c. Investigator-sponsors will comply with paragraphs a and b above.

d. The procedures outlined in appendix B will be followed by U.S. Army Medical Center (MEDCEN) investigators and all MTFs that receive, from MEDCENs, patients on

investigational new drug protocols.

e. The medical monitor as defined in AR 70-25 will:

(1) Be a qualified physician, other than the principal investigator (PI), who is not associated with the protocol for which he or she would be the medical monitor, who is able to provide medical care to research participants for conditions that may arise during the conduct of the study, and who will monitor the participants during the conduct of the study. For investigational new drug and device protocols involving dental products, a qualified dentist may serve as medical monitor if endorsed by the HSRRB or CIRO as appropriate.

(2) Discuss the protocol with the PI and become thoroughly familiar with the protocol's procedures, risks, and inclusion/exclusion criteria.

(3) Review all serious and unexpected adverse events [per ICH (E6) definitions] and all unanticipated adverse device effects (per 21 CFR 812.3 definition) associated with the protocol and provide an unbiased written report of the event to the IRB of record, TSG's HSRRB and the sponsor within 10 calendar days of the initial report. At a minimum, the medical monitor will comment on the outcomes of the adverse event or device effect and its relationship to the investigational new drug or device. The medical monitor will also indicate whether he/she concurs with the details of the report provided by the study investigator.

(4) Depending on the nature of the study, the medical monitor may be assigned to assess one or more of the following phases of a research project: recruitment of participants, enrollment of participants, data collection, or data storage and analysis.

(5) At the discretion of the IRB of record, the medical monitor may be assigned to discuss research progress with the principal investigator, interview participants, consult on individual cases, or evaluate adverse event reports. Medical monitors shall promptly report discrepancies or problems to the IRB. They shall have the authority to stop a research study in progress, remove individual participants from a study, and take whatever steps are necessary to protect the safety and well being of research participants until the IRB can assess the medical monitor's report.

(6) The name and curriculum vitae of the medical monitor must be provided at the time of initial submission of the protocol to the IRB of record and to the HSRRB. The HSRRB must approve changes in medical monitors.

f. TSG's HSRRB members will:

(1) Review and recommend to TSG the approval, approval with modifications, or disapproval of research protocols involving investigational new drugs or devices for which DA is the investigational new drug or device sponsor.

(2) Review and recommend to TSG the approval, approval with modifications, or disapproval of research protocols involving investigational new drugs or devices conducted under RDT&E programs regardless of the individual or agency sponsoring the investigational new drug or device. This review authority extends to DOD-sponsored research that is conducted or managed by USAMRMC.

g. Institutions/Laboratories/Treatment Facilities in which IND/IDE research is conducted must have an assurance of protection of human research participants with either the Department of Defense or the Department of Health and Human Services Office of Human Research Protection. The assurance (multiple project assurance,

single project assurance, or federal wide assurance) requires that research investigators, IRB members and staff, and other relevant personnel maintain continuing knowledge of, and comply with relevant Federal regulation, other applicable guidance, State and local law, and institutional policies for the protection of human participants in research. The institution and the designated IRB will require documentation of such training from research investigators as a condition for conducting DoD supported research involving human participants.

## Chapter 3 Submission of Investigational New Drug Applications and Investigational Device Exemptions

### 3-1. General guidance

- a. In order to use investigational new drugs or significant-risk devices in clinical investigations or human research protocols, the PI must have an approved IND or IDE. The sponsor of the IND or IDE is responsible for filing the IND or IDE with the FDA and for all subsequent correspondence and recordkeeping associated with the IND or IDE. Records of INDs or IDEs maintained by DA agencies will be maintained in accordance with applicable federal regulations and AR 25-400-2. In addition, all required reporting for INDs and IDEs must comply with 21 CFR 312, 21 CFR 812, this regulation, the ICH Guideline for Industry: Structure and Content of Clinical Study Reports (E3) and the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6).
- b. The format for submission and a detailed description of IND requirements are published in 21 CFR 312.
- c. The format for submission and a detailed description of IDE requirements are published in 21 CFR 812. General information regarding the FDA regulation of medical devices is provided at Appendix D of this regulation.
- d. The clinical investigation or research protocol that describes how an investigational new drug or device will be investigated in humans is a portion of the IND or IDE. Procedures for submission and approval of human use protocols are addressed in chapter 4 of this regulation.
- e. Contact RCQ for specific guidance on submission of DA sponsored INDs and IDEs.

### **3-2. Department of Army sponsored investigational new drug applications or investigational device exemptions**

a. Submission and management of a DA sponsored IND or IDE is the responsibility of the Commander, USAMRMC.

b. Coordination of the preparation of a DA sponsored IND or IDE is the responsibility of the respective product manager. The IND or IDE is then forwarded to the RCQ at mailing address Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012. The Deputy for Regulatory Compliance and Quality submits the IND or IDE to the appropriate office of the FDA and is responsible for preparing and maintaining records of all communications with the FDA concerning DA sponsored INDs or IDEs.

### **3-3. Non-Department of the Army (non-DA) sponsored investigational new drug applications or investigational device exemptions**

For a non-DA sponsored IND or IDE, the sponsor is usually a commercial pharmaceutical or device manufacturer. The IND or IDE sponsor will submit the IND or IDE to the FDA and is responsible for all correspondence with the FDA concerning the IND or IDE. Investigators must obtain from the non-DA sponsor a copy of the current investigator's brochure to include in the IRB and TSG's HSSRB review process.

### **3-4. Investigator-sponsored investigational new drug applications or investigational device exemptions**

a. An individual investigator may sponsor an IND or IDE. In this circumstance, the investigator will apply directly to the FDA to obtain FDA approval to use the investigational drug or device. The investigator-sponsor will prepare and maintain

records of all correspondence with the FDA.

b. If the investigator-sponsor is an active duty member or civilian employee of USAMRMC, an information copy of the IND or IDE submission and any subsequent correspondence with the FDA will be sent to the Office of Regulatory Compliance and Quality, USAMRMC, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012.

c. If the investigator-sponsor is an active duty member or civilian employee of any other organization within MEDCOM an information copy of the IND or IDE submission and any subsequent correspondence with the FDA will be sent to Clinical Investigation Regulatory Office, ATTN: MCCS-GCI, Fort Sam Houston, TX 78234-6125.

## Chapter 4

### Procedures for Use of Investigational New Drugs and Devices in U.S. Army Military Treatment Facilities, Dental Treatment Facilities, and Research, Development, Test and Evaluation Facilities

#### **4-1. General guidance**

The acceptance by the FDA of an IND or IDE submission alone does not constitute approval to conduct research or clinical investigations with investigational new drugs or devices in Army facilities. This approval must be obtained as described below depending on the sponsorship of the IND or IDE and the source of funding for the research. For example, conduct of a study at an Army MTF or DTF may involve funding provided or managed by USAMRMC. For an overview of the approval process, refer to Figure 4-1, IND/IDE Protocol Approval Process.

#### **4-2. Approval of protocols conducted with a Department of the Army sponsored investigational new drug or device**

a. For research conducted in a MTF and DTF, research may not begin until the protocol is -

(1) Reviewed by the scientific and ethical review committees of the MTF where the investigation will be conducted. If the research is to be conducted at an MTF or DTF that does not have scientific and ethical review committees, these reviews can be accomplished at the Regional Medical Command under which the MTF or DTF is affiliated.

(2) Reviewed and approved by the commander of the MTF or DTF where the investigation will be conducted.

(3) Reviewed and approved by the commander of the Regional Medical Command where the investigation will take place.

(4) Reviewed and approved by the CIRO at Commander, U.S. Army Medical Department Center & School, Clinical Investigation Regulatory Office, ATTN: MCCS-GCI, 1608 Stanley Road, Fort Sam Houston, TX 78234-6125.

(5) Forwarded to RCQ at Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012.

(6) Reviewed and recommended for approval by TSG's HSRRB.

(7) Approved by TSG.

(8) Submitted to the FDA by RCQ as part of an original IND or amendment to an existing IND. If the research protocol is part of an original IND, the research cannot begin until 30 days from the date the IND was received by the FDA, unless informed by FDA that the research may begin sooner.

b. For research conducted or managed by an RDT&E organization, research may not begin until the protocol is —

(1) Reviewed and approved by the Commander, USAMMDA.

(2) Reviewed by the scientific and human use committees of the facility conducting the research.

(3) Reviewed and approved by the commander of the facility where the research will be conducted.

(4) Forwarded to RCQ at Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 210702-5012.

(5) Reviewed and recommended for approval by TSG's HSRRB.

(6) Approved by TSG.

(7) Submitted to the FDA by RCQ as part of an original IND or amendment to an existing IND. If the research protocol is part of an original IND, the research cannot begin until 30 days from the date the IND was received by the FDA, unless informed by FDA that the research may begin sooner.

**4-3. Approval of protocols conducted with Non-Department of the Army sponsored investigational new drug or device**

a. For research conducted in a MTF and DTF, the protocol will be—

(1) Reviewed by the scientific and ethical review committees of the MTF or DTF where the research will be conducted. If the MTF or DTF at which the research is to be conducted does not have scientific and ethical review committees, these reviews may be accomplished at the Medical Center or Regional Medical Command with which the MTF or DTF is affiliated.

(2) Reviewed and approved by the commander of the MTF or DTF where the research will be conducted.

(3) Reviewed and approved for the MEDCOM Commander by the CIRO, U.S. Army Medical Department Center & School.

b. If funding is provided by USAMRMC under either Defense Health Program funds or RDT&E funds, the protocol will be—

(1) Forwarded to the RCQ at Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012.

(2) Reviewed by TSG's HSRRB and forwarded to TSG for approval prior to the

start of the clinical investigation.

#### **4-4. Approval of protocols conducted with investigator-sponsored investigational new drugs or devices**

a. For investigator-sponsored clinical investigations conducted in MTFs and DTFs, the protocol will be reviewed and approved as described in paragraph 4-3a.

b. For research conducted or managed by an RDT&E organization, research may not begin until the protocol is reviewed and approved as described in paragraph 4-2b.

#### **4-5. Approval for the investigational use of radiopharmaceuticals**

For approval to use an investigational radiopharmaceutical, the protocol must first be reviewed and approved by a radiation control committee established in accordance with the requirements of TB MED 525. The radiation control committee must have accepted responsibility for enforcement of the requirements of TB MED 525 at the institution at which the research will be conducted. In addition, requirements identified in paragraphs 4-2, 4-3, or 4-4 will be observed.

#### **4-6. National Cancer Institute (NCI) cooperative group protocols and cancer chemotherapy investigational agents**

A physician requesting approval to conduct an investigation under a NCI cooperative group protocol or to use a cancer chemotherapy investigational agent for treatment of individual patients will initiate the investigation or treatment in accordance with directives published by the CIRO.

#### **4-7. Approval of protocol amendments**

Investigators must submit protocol amendments to the IRB of record for approval.

Before implementation, protocol amendments must also receive review and approval

through the HSRRB and/or CIRO as appropriate. The product manager must also receive a copy of the approved protocol amendment for DA sponsored INDs or IDEs.

#### **4-8. Treatment use of an IND**

a. A physician, seeking approval for one-time use of an investigational drug for a patient in a situation where there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient (a treatment IND), must contact the agency or individual sponsoring the IND to obtain the drug. If the sponsor agrees to release the drug for treatment use, it is the sponsor's responsibility to obtain permission from the FDA to supply the drug to the requesting physician.

b. Before the investigational new drug may be used in a MTF, the physician must, through the IRB of record and MTF commander, obtain the approval of the MEDCOM commander or designee. Within MEDCOM MTFs, requests for treatment use of investigational new drugs should be directed to the Commander, U.S. Army Medical Department Center & School, Clinical Investigation Regulatory Office, ATTN: MCCS-GCI, 1608 Stanley Road, Fort Sam Houston, TX 78234-6125, DSN 471-2511/9302. Within 18th MEDCOM, requests should be directed to RCQ at Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012. Requests must include the patient's name; the diagnosis; the drug name, quantity, and source; the medical officer responsible for the patient; and the nature of the treatment use of the IND. In cases where approval is granted, CIRO will forward, as necessary, the information to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street,

Fort Detrick, MD 21702-5012.

c. It is the responsibility of the treating physician to obtain approval of the appropriate clinical investigation committee and IRB of the use of the investigational new drug.

d. In cases where the one-time treatment use is approved, the treating physician will send a report summarizing the case to the CIRO, USAMRMC RCQ, and the sponsor of the IND. In addition to describing the circumstances and outcome of the use of the investigational new drug, the physician will include copies of any forms or reports furnished to a commercial manufacturer, other non-DA agency, or an individual in connection with the case.

#### **4-9. Emergency use of an IND**

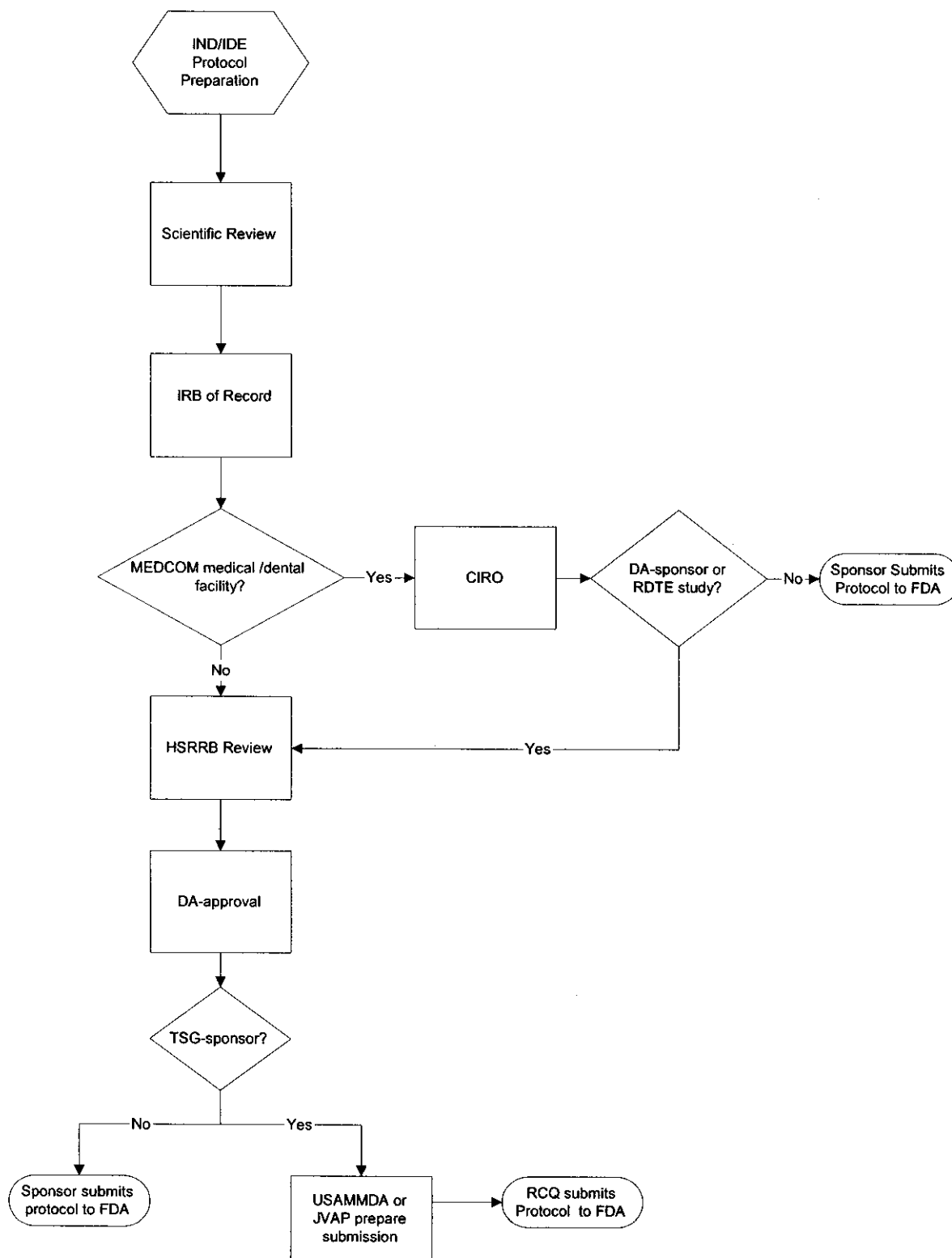
When the need for an investigational new drug arises in an emergency situation that does not allow time for submission of a treatment IND in accordance with paragraph 4-7, such use must be in accordance with 21 CFR 312.36. Notifications specified in paragraph 4.7 will be fulfilled retrospectively.

#### **4-10. Continuing review of research**

In accordance with 21 CFR 56.109(f), the IRB of record shall conduct continuing review of research at intervals appropriate to the degree of risk, but no less than once per year. The investigator is responsible for submitting to the IRB of record the required report of research activities prior to the scheduled review date. In conducting continuing review of research, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers

should also receive a copy of the complete protocol including any modifications previously approved by the IRB. Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB. A copy of the approved continuing review report and minutes documenting the review from the IRB of record should be submitted to the second level of review – CIRO and/or HSRRB – that has responsibility for review of the protocol.

Figure 4-1 (IND/IDE Protocol Approval Process)



## Chapter 5 Investigational Drug and Device Use Control

### 5-1. Procurement and storage

Investigational new drugs and devices are the property of the sponsor throughout the study.

a. Storage of investigational new drugs in MTFs. The pharmacy is the appropriate storage area for all investigational new drugs in MTFs. Appendix B contains instructions for the control of investigational new drugs used to treat patients returning to an MTF from a MEDCEN. The pharmacy is responsible for the proper recording, periodic inventory verification, labeling, storage, and dispensing of investigational new drugs in accordance with the investigator's written orders. The dispensing of investigational new drugs should be integrated with the rest of the inpatient or outpatient drug distribution system with respect to packaging, labeling, order receiving, profile maintenance, inventory checks, and delivery. To comply with 21 CFR 312.61 and the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6), section 4.6.5, the storage of investigational new drugs must be separate from the regularly stocked drugs in the pharmacy and identified in such a way that minimizes the risk of being dispensed as a regularly stocked drug.

b. Storage of radiopharmaceutical investigational new drugs and devices. Radiopharmaceutical dosage forms should be stored in the nuclear medicine service's area if appropriate security is provided. The preferred area for storing radiopharmaceuticals is a nuclear pharmacy co-located with the nuclear medicine service. If storage in the nuclear medicine service area is not possible, the radiopharmaceutical may be stored in the pharmacy. The nuclear medicine service

would be responsible for proper recordkeeping, labeling, storage, and handling of the radiopharmaceuticals subject to appropriate regulations.

c. Storage of investigational new drugs at RDT&E Facilities. The commander or director of research facilities (such as laboratories) that do not have a pharmacy will appoint a specific custodian to maintain accountability for all investigational new drugs as noted above. If the research facility is located near an MTF with a pharmacy, it is recommended that the research facility commander or director pursue a cooperative agreement with the MTF commander to use the MTF pharmacy as custodian of investigational new drugs. Access to the investigational new drug within RDT&E facilities should be limited to those individuals directly involved in the research use of the investigational new drug.

d. Recordkeeping. Other than for radiopharmaceuticals, as noted in paragraph 5-1b, a complete record of each investigational new drug will be maintained by the pharmacy or appointed custodian and will contain the following information:

- (1) Name of drug, dosage form, and strength (or proper identification if blinded).
- (2) Title of protocol under which drug is used.
- (3) Signed copy of Form FDA 1572 with the name(s) of investigator(s).
- (4) Manufacturer or other source of drug.
- (5) Amount of drug and date received.
- (6) Perpetual inventory record of on-hand stocks of drug.
- (7) Expiration date (if available).
- (8) Lot or control number.

(9) Name(s) of participant(s) and drug, plus lot or control number for each dispensing.

(10) Date(s) on which participant(s) receive drug and quantity dispensed.

(11) Initials of dispensing official.

(12) Point of contact and procedures for emergency unblinding, if applicable.

e. Investigational device use control. Investigational device storage, security, and recordkeeping requirements are determined based on the nature and use of the device. The PI or a designated representative will act as custodian of the device. Within MTFs, the Chief, Clinical Support Division will maintain a listing of investigational devices in use in the hospital, their lot or control numbers, and the custodians for each device.

f. Security. Security requirements for investigational new drugs will be the same as those recognized for security of prescription drugs or drugs under Drug Enforcement Agency (DEA) control, if applicable. Security requirements for storage of pharmaceuticals are identified in AR 40-61, Medical Logistics Policies and Procedures.

g. Discrepancies. The custodian of the investigational new drug record will resolve discrepancies in inventory record balances and on-hand balances. Discrepancies unable to be resolved by the custodian will be reported to the PI and sponsor.

## **5-2. Prescribing and dispensing**

a. Authorization to prescribe. Personnel authorized prescribing privileges in accordance with AR 40-68 may prescribe investigational new drugs and devices. Non-physician prescribers must be appropriately credentialed and approved by their local commander to prescribe investigational new products. These prescribing limitations must be stated in the credentialing documentation.

b. Prescribing and dispensing investigational new drugs and devices in MTFs.

The Pharmacy Service or other designated investigational new drug or device custodian will dispense investigational new drugs or devices as ordered on DD Form 1289 (DOD Prescription) or DA Form 4256 (Doctor's Orders) signed by the PI or a subinvestigator listed on Form FDA 1572 (for investigational new drug). A copy of the Form FDA 1572 must be located in the dispensing area (i.e., pharmacy) to verify the authenticity of the prescriber's signature.

c. Prescribing and dispensing investigational new drugs and devices in RDT&E facilities. Prescribing and dispensing of investigational new drugs or devices to study participants will be documented on case report forms that are part of the research record for each individual participant. The signature of the investigator or custodian on the case report form will document the dispensing of the investigational product. Research protocols or standard operating procedures will identify individuals authorized to dispense investigational products.

d. Labeling. In addition to labeling requirements specified in AR 40-3 for dispensed medications, the immediate package of an investigational new drug shall bear a label with the statement, "Caution: New Drug – Limited by Federal (or United States) law to investigational use," in accordance with 21 CFR 312.6. Similarly, in accordance with 21 CFR 812.5 the label of an investigational device for use in diagnosis must include the statement, "Caution – Investigational device. Limited by Federal law to investigational use."

### **5-3. Administration of investigational new drugs and devices**

The principal investigator is responsible for providing nurses and other healthcare

professionals who administer investigational new drugs with the necessary information about basic pharmacology, storage, adverse effects, precautions, authorized prescribers, patient monitoring guidelines, and overall study objectives and procedures. This information is generally available in the investigator's brochure for the specific investigational new drug. For investigational devices, users will be trained in the use of the device and will have adequate knowledge of necessary calibration, application, and general use procedures for the device.

#### **5-4. Regulatory files**

Records for DA sponsored investigational new drugs and devices will be maintained in accordance with the requirements identified in the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6), section 8. All regulatory files are subject to review by additional authorities, including representatives of the FDA, and other appropriate and authorized entities such as sponsor designated clinical research monitors and auditors.

#### **5-5. Drug information**

The commander of the facility in which the research is being conducted will establish a central unit where basic essential information on investigational new drugs is maintained and can be made available to all authorized personnel. In MTFs, the pharmacy is the appropriate location for such a drug information center. The Pharmacy and Therapeutics Committee should act as the monitor of available information. At a minimum, information normally in the investigator's brochure (dosage, indications, expected effects, potential untoward effects, contraindications, storage requirements, preparation and administration instructions) and names and telephone numbers of

principal and authorized subinvestigators should be made available to personnel who administer investigational new drugs. For studies involving masked (blinded) test articles, procedures for breaking the mask code will also be available. Arrangements must be made to have required information available 24 hours a day.

#### **5-6. Device information**

The custodian of an investigational device will establish an information file for the device. This file will contain all the following information as applicable:

- a. Investigator's Brochure or the name of device (or proper identification if blinded), indications, expected effects, potential untoward effects, contraindications and storage requirements.
- b. Preparation and administration instructions.
- c. Title of protocol under which device is used.
- d. Signed copy of Investigator's Agreement with the name(s) of investigator(s).
- e. Manufacturer or other source of device.
- f. Amount of device(s) and date received.
- g. Perpetual inventory record of on-hand stocks of device.
- h. Expiration date (if available).
- i. Lot or control number.
- j. Name(s) of participant(s) and drug, plus lot or control number for each dispensing.
- k. Date(s) on which participant(s) receive/use device and quantity dispensed.
- l. Initials of dispensing official.
- m. Point of contact and procedures for emergency unblinding, if applicable.

**5-7. Retention period**

The FDA requires in 21 CFR 312.57 and 21 CFR 812.140 that all research records involving an investigational new drug or device be kept for a minimum of two years after the date a marketing application is approved to investigate the drug for a specified indication. If no application is to be filed or if the application is not approved for such indication, all records will be maintained for a minimum of two years after the investigation is discontinued and the FDA is notified. See AR 25-400-2 (file no. 40-38a or 70-25a) found at <http://www.usapa.army.mil> for additional recordkeeping requirements for medical and research records.

## Chapter 6 Special Considerations

### 6-1. Reporting of adverse events with investigational new drugs

a. Definitions. For the purpose of defining adverse events with investigational new drugs, this regulation follows the definitions provided in the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6) and ICH Guideline for Clinical Safety Data Management (E2A). For purposes of this regulation, the term “patient” is used to apply to all research participants. The definitions are as follows:

(1) Adverse event. An adverse event is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

(2) Serious adverse event. Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

(3) Unexpected adverse drug reaction. An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator’s Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

b. Procedures for reporting serious and unexpected investigational new drug

## adverse events

(1) An investigator who observes or learns of a serious and unexpected adverse event from an investigational new drug will, at the time of discovery, notify the sponsor of the investigational new drug. A written report will follow the initial notification within three working days. For a DA sponsored investigational new drug, this notification will be made to RCQ at Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012 (DSN 343-2165, Commercial (301) 619-2165). The facsimile number is DSN 343-7803, Commercial (301) 619-7803. Additionally, the investigator will notify the applicable product manager.

(2) The investigator will also notify all IRBs that reviewed and approved the research protocol. Such reports will be submitted within time frames established by the respective IRBs.

(3) Investigators will use protocol-specific case report forms for submitting adverse event reports. If there is not a specific case report form for adverse events, the FDA Form 3500 (MedWatch) will be used.

(4) For those serious and unexpected adverse event(s) judged by the product manager and Deputy, RCQ to be associated with the use of the investigational new drug, the product manager (through Deputy, RCQ) will submit to the FDA an IND safety report. For an unexpected fatal or life-threatening experience associated with the use of the investigational new drug, this report will be by telephone or facsimile as soon as possible, but in no event later than seven calendar days after the sponsor's initial receipt of the information. For other serious and unexpected experiences associated

with the use of the investigational new drug, the report will be in writing within 15 calendar days of the sponsor's initial receipt of the information. An IND safety report made to the FDA by telephone or facsimile will be followed by a written IND safety report submitted within 15 calendar days of the initial telephone or facsimile report.

(5) The sponsor will notify all participating investigators of all IND safety reports.

(6) The sponsor (through RCQ) will submit to FDA and all participating investigators follow-up information to an IND safety report as soon as the relevant information is available.

c. All other adverse events from IND research will be reported to the IRB of record in accordance with local procedures. The IND annual report submitted to the sponsor and the continuing review report submitted to the IRB of record will contain a compilation of all adverse events and the respective outcomes associated with the product during the course of the year.

## **6-2. Reporting of unanticipated adverse device effects**

a. Definition. For the purpose of defining "unanticipated adverse device effect", this regulation follows the definition provided in 21 CFR 812.3. Unanticipated adverse device effect is defined as a serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

b. Procedures for reporting unanticipated adverse device effects

(1) An investigator who observes an unanticipated adverse device effect will notify the sponsor as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. For a DA sponsored investigational device, this notification will be made to RCQ at Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012 (DSN 343-2165, Commercial (301) 619-2165). The facsimile number is DSN 343-7803, Commercial (301) 619-7803.

(2) The investigator will also notify all reviewing IRBs that reviewed and approved the research protocol. Such reports will be submitted within the timeframes established by the respective IRBs. In addition, MTF investigators will submit adverse events to the MTF Pharmacy and Therapeutics Committee in accordance with AR 40-3.

(3) The sponsor will immediately conduct an evaluation and if it is determined that the device effect presents an unreasonable risk to participants will terminate the study or parts of the study not later than 5 working days after this determination has been made and not later than 15 working days after the sponsor first received notice of the effect. The sponsor will also submit a report on its evaluation to the FDA, all reviewing IRBs, and participating investigators with 10 working days after first receiving notice of the effect. Thereafter, additional reports will be submitted as FDA requests.

(4) If the device is a significant-risk device, resumption of the terminated study may not begin without both IRB and FDA approval.

c. All other adverse events from IND research will be reported to the IRB of record in accordance with local procedures. The IND annual report submitted to the sponsor and the continuing review report submitted to the IRB of record will contain a

compilation of all adverse events and the respective outcomes associated with the product during the course of the year.

### **6-3. Use of a marketed drug for an unapproved indication in clinical practice**

Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner, when the intent is the practice of medicine, does not require the submission of an IND application.

However, when a physician uses an approved drug for an unapproved indication and systematically records data on the drug's effects in order to substantiate or refute a claim of therapeutic efficacy for the unapproved indication, the physician is conducting a clinical investigation. In these situations, the physician-investigator must adhere to the requirements of AR 40-38 (for clinical investigations) or AR 70-25 (for RDT&E research) in conducting the investigation. According to 21 CFR 312, such a clinical investigation of a drug product that is lawfully marketed in the United States must be done under an IND, unless all of the following apply:

- a. The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use, nor is it intended to be used for any other significant change in the labeling of the drug.
- b. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the investigation is not intended to support a significant change in the

advertising for the product.

c. The investigation does not involve a route of administration, a dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

d. The investigation is conducted in compliance with the requirements for human use review and informed consent set forth in 21 CFR 50, 21 CFR 56, 32 CFR 219, and AR 40-38 (for clinical investigations) or AR 70-25 (for RDT&E research).

e. The drug is not represented in a promotional context as being safe or effective for the purposes for which it is being investigated.

For research in which the interpretation of the requirements for an IND are not clear, the IRB of record, CIRO, or the HSRRB may request that the investigator obtain written documentation from the FDA regarding the need for an IND.

#### **6-4. Use of investigational new drugs and approved drugs for unapproved indications as part of a military contingency operation**

Section 1107, Title 10 of the United States Code (10 USC 1107) describes specific requirements for use of investigational drugs and approved drugs for unapproved indications in military contingency operations. This statute applies whenever the Secretary of Defense requests or requires a member of the armed forces to receive an investigational new drug or a drug unapproved for its applied use. The statute establishes the President as the approving authority for the administration of unapproved drugs without informed consent. The statute requires that prior to the drug's first administration, service members must be provided with written notice containing specific information. The required information includes what the drug is; why

it is being administered; possible side effects, including interactions with other drugs or treatments being administered to the members receiving the investigational new drug or drug for an unapproved use; and other information the Secretary of Health and Human Services may require to be disclosed. The Secretary of Defense is required to ensure that health care providers who administer or treat members who have received an investigational new drug or a drug unapproved for its applied use receive certain information. The required information includes information on possible side effects as well as any other information the Secretary of Health and Human Services may require. The implementing instructions for 10 USC 1107 are described in 21 CFR 50.23(d) (Informed Consent of Human Subjects-Exception from General Requirements) (published in the Federal Register on October 5, 1999 at 64 FR 54180), Executive Order 13139 (Improving Health Protection of Military Personnel Participating in Particular Military Operations) (published in the Federal Register on September 30, 1999 at 64 FR 54175), and DOD Directive 6200.2, dated August 1, 2000 (Use of Investigational New Drugs for Force Health Protection).

#### **6-5. Emergency procurement of drugs and biologicals from foreign suppliers**

##### **a. Emergency procurement of drugs**

(1) It is the policy of TSG that drugs used in an Army MTF will be approved by the FDA and procured from suppliers in the United States. However, it is recognized that situations may arise when a drug cannot be procured in a timely manner from a supplier in the United States, especially in an MTF located outside the continental United States. If an FDA approved drug is unavailable from a U.S. supplier, drugs distributed by foreign suppliers may be procured, provided one of the following

circumstances exists:

(a) The drug is needed to save life, limb, or eyesight and the time required to procure the drug from a U.S. supplier would endanger the patient's well being.

(b) The drug is needed to continue life sustaining chronic therapy and the time required to procure the drug from a U.S. supplier would cause an interruption of such therapy as to endanger the patient's well being.

(2) Drugs purchased from foreign suppliers must contain the same active ingredient(s) and be formulated in the same dosage form as the like product procured from a U.S. supplier. If the active ingredient or dosage form of a drug procured from a foreign supplier is not available in the United States, the drug is considered investigational and procedures for use of an investigational drug apply.

(3) The procedures for emergency procurement of drugs from foreign suppliers are as follows:

(a) The Chief, Pharmacy Services will initiate the request for purchase of a drug from a foreign supplier when professional judgment necessitates such a purchase.

(b) The MTF commander or designee will sign all purchase requests for drugs from a foreign supplier.

(c) The Chief, Pharmacy Services will maintain a record of use for drugs procured from a foreign supplier. A copy of this record will be forwarded to the Commander, U.S. Army Medical Department Center & School, Clinical Investigation Regulatory Office, ATTN: MCCS-GCI, 1608 Stanley Road, Fort Sam Houston, TX 78234-6125 within 5 working days after the drug is procured from the foreign supplier. For 18th MEDCOM, the record will be forwarded to RCQ at Commander, U.S. Army

Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012. A copy of the record will also be presented to the Pharmacy and Therapeutics Committee at the MTF at the next regularly scheduled meeting. This record will consist of the drug's trade name, generic name, manufacturer, lot number, expiration date, amount, and source; a brief justification of why procurement of the drug from a foreign supplier was necessary; and an identifier for the patient (e.g., initials, last 4 of SSN) who received the drug procured from a foreign supplier.

b. Emergency procurement of vaccines and biological products

Vaccines and other biological products may not be procured from foreign suppliers if the same vaccine or biological product is available from a U.S. supplier. If there is a need to procure a vaccine or biological product that is not available from a supplier in the United States, the vaccine or biological product is considered investigational and procedures for use of an investigational drug apply.

c. Procedures for emergency use of an IND are described in paragraph 4-8.

**6-6. Use of Schedule I controlled substances**

a. Clinical use of Schedule I controlled substances

(1) For approval to use a Schedule I controlled substance in human participants, a protocol will be submitted as described in paragraph 4-2. A statement of the security, audit, and control provisions for the Schedule I controlled substance will accompany the protocol and IND submissions (e.g., the investigators' brochure would describe security requirements).

(2) The sponsor of the IND will provide the investigator with the following statement:

I hereby certify that on (date), pursuant to 21 USC 355(i) and 21 CFR 312.1, I, (name and address of IND sponsor) submitted an Investigational New Drug application to the Food and Drug Administration for: (Name of investigational drug)(Date) (Signature of applicant).

(3) For a DA sponsored IND, the statement will be provided by the Office of Regulatory Compliance and Quality at Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012.

(4) The statement will be forwarded in triplicate by the investigator along with a Drug Enforcement Administration Certificate of Registration (DEA Form 225) to Drug Enforcement Administration, Department of Justice, Office of Diversion Control, ATTN: Registration Unit, Washington, DC 20537.

b. Nonclinical animal use of Schedule I controlled substances

(1) In order to conduct nonclinical animal research with Schedule I controlled substances, the investigator will submit DEA Form 225 along with three copies of the research protocol to Drug Enforcement Administration, Department of Justice, P.O. Box 28083, Central Station, Washington, DC 20038-8083. The research protocol should provide the following information:

(a) Investigator's name, address, and current DEA registration number, if any

(b) Institutional affiliation of the researcher

(c) Qualifications of the investigator, including curriculum vitae and an appropriate list of publications

- (d) Title of the study
  - (e) Statement of the purpose of the research
  - (f) Name and amount of controlled substance(s) involved
  - (g) Description of the research to include the species and number of research animals, dosage to be administered, route and method of administration, and duration of the project
  - (h) Location where the research will be conducted
  - (i) Statement of security provisions for storing the controlled substance(s) in order to prevent diversion
  - (j) Proof of institutional approval to conduct the research
  - (k) Indication of an approved, funded grant, if any
- (2) The investigator will also comply with the provisions of AR 70-18.

## Appendix A References

### Section I Required Publications

AR 11-2  
Management Control. (Cited in Army Management Control process statement and Appendix C.)

AR 25-400-2  
The Modern Army Recordkeeping System (MARKS). (Cited in paras 3-1 and 5-7.)

AR 40-3  
Medical, Dental, and Veterinary Care. (Cited in paras 5-2 and 6-1.)

AR 40-38  
Clinical Investigation Program. (Cited in paras 1-4, 2-2, 2-5, 2-6, 2-9, 4-1, 5-1, and 6-2 and in the Glossary.)

AR 40-61  
Medical Logistics Policies and Procedures. (Cited in para 2-5, 2-9, and 5-1.)

AR 70-18  
SECNAVINST 3900.38B/AFR 169-2/DARPAINST 18/DNAINST 3216.1B/USUHSINST 3203.  
The Use of Animals in DOD Programs. (Cited in paras 1-4 and 6-6.)

AR 70-25  
Use of Volunteers as Subjects of Research. (Cited in paras 1-4, 2-2, 2-4, 2-6, 2-7, 2-9, 2-9, 4.1, 5-1, and 6-2.)

AR 70-65  
Management of Controlled Substances, Ethyl Alcohol, and Hazardous Biological Substances in Army Research, Development, Test, and Evaluation Facilities. (Cited in paras 2-7 and 2-9.)

DOD Directive 3216.1  
Use of Laboratory Animals in DOD Programs. (Cited in para 1-4.)  
Available through <http://www.dtic.mil/whs/directives>.

DOD Directive 3216.2  
Protection of Human Subjects and Adherence to Ethical Standards in DOD-Supported Research. (Cited in para 1-4 and in the Glossary.) Available through <http://www.dtic.mil/whs/directives>.

**DOD Directive 6200.2**

Use of Investigational New Drugs for Force Health Protection. (Cited in para 6-4.)  
Available through <http://www.dtic.mil/whs/directives>.

**Executive Order 13139**

Executive Order 13139 of September 30, 1999-Improving Health Protection of Military Personnel Participating in Particular Military Operations. (Cited in para 6-4.)  
Available from the Federal Register Online via GPO Access. Web site  
[http://www.access.gpo.gov/su\\_docs/aces/aces140.html](http://www.access.gpo.gov/su_docs/aces/aces140.html)

**21 CFR 50**

Protection of Human Subjects. (Cited in paras 1-4, 2-9, 6-3 and 6-4.) Available via  
<http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>. This page allows the reader to access, by Title, both current and historical CFR volumes.

**21 CFR 54**

Financial Disclosure by Clinical Investigators. (Cited in para 2-9.) Available via  
<http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>. This page allows the reader to access, by Title, both current and historical CFR volumes.

**21 CFR 56**

Institutional Review Boards. (Cited in paras 4-10 and 6-3.) Available via  
<http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>. This page allows the reader to access, by Title, both current and historical CFR volumes.

**21 CFR 312**

Investigational New Drug Application. (Cited in paras 2-2, 2-4, 2-7, 2-9, 3-1, 5-2 and 5-7.) Available via <http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>. This page allows the reader to access, by Title, both current and historical CFR volumes.

**21 CFR 812**

Investigational Device Exemptions. (Cited in paras 2-2, 2-4, 2-7, 2-9, 3-1, 5-2, 5-7, 6-2, Appendix D and the Glossary.) Available via <http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>. This page allows the reader to access, by Title, both current and historical CFR volumes.

**32 CFR 219**

Protection of Human Subjects. (Cited in para 1-4, 2-2, 2-11 and 6-2.) Available via  
<http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>. This page allows the reader to access, by Title, both current and historical CFR volumes.

**ICH Guideline for Good Clinical Practice: Consolidated Guideline**

The International Conference on Harmonization Guideline for Good Clinical Practice: Consolidated Guideline (E6) (Cited in paras 2-9, 4-1, 5-1 and Glossary.) as published by the FDA in the Federal Register at 62 FR 25691 (May 9, 1997). Available via

<http://www.fda.gov/cder/guidance/iche3.pdf> or from the Federal Register Online via GPO Access (a searchable database) at [http://www.access.gpo.gov/su\\_docs/aces/aces140.html](http://www.access.gpo.gov/su_docs/aces/aces140.html).

ICH Guideline for Industry: Structure and Content of Clinical Study Reports (E3) (Cited in para 2-9. Available via <http://www.fda.gov/cder/guidance/iche3.pdf>.

#### 10 USC 1107

Notice of use of an investigational new drug or a drug unapproved for its applied use. (Cited in para 6-4). Available via searchable database at web site <http://uscode.house.gov/usc.htm>.

## Section II

### Referenced Publications

A related publication is merely a source of additional information. The user does not have to read it to understand this regulation.

#### TB MED 525

Control of Hazards to Health from Ionizing Radiation Used by the Army Medical Department. Available via <http://chppm-www.apgea.army.mil/>. This page opens to the U.S. Army Center for Health Promotion and Preventive Medicine. The regulation can be accessed through the publications section of the page.

#### 21 CFR 314

Applications for FDA Approval to Market a New Drug. Available via <http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>. This page allows the reader to access, by Title, both current and historical CFR volumes.

#### 21 CFR 361.1

Radioactive Drugs for Certain Research Uses. Available via <http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>. This page allows the reader to access, by Title, both current and historical CFR volumes.

#### 21 CFR 1301

Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances. Available via <http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>. This page allows the reader to access, by Title, both current and historical CFR volumes.

#### 21 CFR 1308.11

Schedules of Controlled Substances, Schedule I. Available via <http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>. This page allows the reader to access, by Title, both current and historical CFR volumes.

#### 45 CFR 46

Protection of Human Subjects. Available via <http://www.access.gpo.gov/nara/cfr/cfr->

table-search.html#page1. This page allows the reader to access, by Title, both current and historical CFR volumes.

#### 21 USC 321

Federal Food, Drug, and Cosmetic Act, Subchapter II, Definitions. Available via searchable database at: <http://uscode.house.gov/usc.htm>.

#### 21 USC 355

Federal Food, Drug, and Cosmetic Act, Subchapter V, Drugs and Devices. Available via searchable database at: <http://uscode.house.gov/usc.htm>.

Food and Drug Administration Information Sheets. Guidance for Institutional Review Boards and Clinical Investigators. Available via <http://www.fda.gov/oc/ohrt/irbs/default.htm>.

National Bioethics Advisory Commission. Report of 30 April 2001 entitled, "Ethical and Policy Issues in Research Involving Human Participants." Available via <http://bioethics.georgetown.edu/nbac/pubs.html>.

National Institutes of Health, Office for Protection from Research Risks. Protecting Human Research Subjects, Institutional Review Board Guidebook. Available via [http://ohrp.osophs.dhhs.gov/irb/irb\\_guidebook.htm](http://ohrp.osophs.dhhs.gov/irb/irb_guidebook.htm).

### Section III

#### Prescribed Forms

This section contains no entries.

### Section IV

#### Referenced Forms

##### DA Form 4256

Doctor's Orders

##### DD Form 1289

DOD Prescription

##### DEA Form 225

Drug Enforcement Administration Certificate of Registration. (This form can be obtained from Drug Enforcement Administration, Department of Justice, Post Office Box 28083, Central Station, Washington, DC 20038-8083.)

##### Form FDA 1571

Investigational New Drug Application (IND). (This form can be downloaded from <http://forms.psc.gov/forms/FDA/fda.html>.)

**Form FDA 1572**

Statement of Investigator. (This form can be downloaded from <http://forms.psc.gov/forms/FDA/fda.html>.)

**Form FDA 3500**

MedWatch: For voluntary reporting by healthcare professionals of adverse events and product problems. (This form can be downloaded from <http://www.fda.gov/medwatch/online/medwatch.pdf>.)

**Form NIH 2564**

Investigational Agent Accountability Record.  
(<http://ctep.info.nih.gov/forms/index.html#requisition>)

## Appendix B

### Control of Investigational Drugs Used to Treat Patients Returning to a Military Treatment Facility from a United States Army Medical Center

#### B-1. Basic principles

a. This appendix generally refers to the transfer of patients enrolled in oncology treatment protocols from a medical center within a Regional Medical Command to a U.S. Army Medical Department Activity (MEDDAC) within that Regional Medical Command. However, there are some situations in which patients are transferred between Regional Medical Commands. Therefore, this appendix uses the term “MTF” in referring to the gaining facility to represent the gaining facility as either a MEDDAC or a MEDCEN.

b. Adherence to regulations on use, storage, and control of investigational new drugs outlined in this regulation is important because interstate shipment of all investigational new drugs is subject to Federal Regulation by the FDA.

c. The physician listed as PI on the investigational drug protocol submitted to CIRO is responsible for the conduct of that protocol and for carrying out administrative requirements (for example, continuing reviews) as outlined in this regulation.

d. CIRO must be made aware of any extension of an investigational drug study to an additional MTF.

e. Review and approval of the investigational protocol by a regional Army Medical Center’s scientific and ethical review committees (i.e., Clinical Investigation Committee) for an MTF supported by the Army Medical Center, fulfills the FDA requirements for institutional review. Local commanders may require additional review at their discretion.

f. If a patient enrolled in an investigational new drug protocol is returned to an MTF

that has functioning scientific and ethical review committees, the protocol will require review and approval at the gaining MTF. Investigators should initiate the review process early in the discharge planning process. Gaining facilities should have procedures in place to allow for the continuation of investigation therapy through the duration of the review process.

## B-2. Procedure

When a patient referred to an Army Medical Center from a supported MTF agrees to participate with a treatment protocol involving an investigational new drug and is ready to return to an MTF, the following will be accomplished:

- a. The PI or designee from the referral service at the Army Medical Center (for example, Hematology/Oncology Service) will contact by telephone the receiving physician. They will discuss the patient's treatment follow-up as well as the requirements of the FDA and this regulation pertaining to the use of investigational new drugs. The PI will inform the Clinical Investigation Regulatory Office of the extension of an investigational new drug study to an additional MTF, title of the study, and name of the MTF physician who will be in charge of continuing the patient's therapy. The MTF physician becomes a subinvestigator on the protocol.

- b. The referring physician will mail to the receiving physician a copy of the patient's medical records, a copy of the informed consent forms, a letter of instructions, a copy of the investigational protocol, a copy of the investigator's brochure, and Form FDA 1572 (Statement of Investigator). Figure B-1 provides an example memorandum. Please note that this is only an example. Titles, departments, and other specific information need to be changed.

c. The receiving MTF physician completes Form FDA 1572 and returns it to the chief of the referring service of the Army Medical Center, who maintains the Form FDA 1572 in the protocol file for reference. The PI at the Army Medical Center will forward the name and curriculum vitae of the MTF physician to the Commander, U.S. Army Medical Department Center & School, Clinical Investigation Regulatory Office, ATTN: MCCS-GCI, 1608 Stanley Road, Fort Sam Houston, TX 78234-6125 and to the appropriate agencies (for example, the NCI) for inclusion in the Form FDA 1572. This information will list the MTF Deputy Commander for Clinical Services, the supervising Chief of Department of Medicine, the Chief of Pharmacy Services, and the Chief of the Clinical Investigation Department, if one is formed at the MTF, to arrange for the patient to receive the investigational drug.

d. Upon receiving a request for an investigational new drug signed by an authorized physician, Army Medical Center pharmacy dispenses a supply of the investigational new drug and ships (requiring signature receipt) it to the Chief, MTF pharmacy, with a copy of the investigational protocol and Investigator's Brochure.

e. The MTF pharmacy will store the investigational new drug(s) until it dispenses the drug(s) to the patient. The MTF pharmacy will also provide appropriate drug-use counseling to the patient, with advice from the Army Medical Center pharmacy as needed.

f. When an additional supply of the investigational new drug(s) is needed, the MTF pharmacy will notify the pharmacy at the Army Medical Center. The medication will be shipped (requiring signature receipt) to the MTF pharmacy where it will be handled as indicated in paragraph B-2e above.

g. If treatment is discontinued, the MTF physician will notify the MTF pharmacy so that any remaining investigational new drugs may be returned to the Pharmacy Service of the Army Medical Center.

h. The MTF physician must provide the referral service at the Army Medical Center with semi-annual follow-up information regarding the progress of the patient. Flow sheets for this purpose will be provided by the Army Medical Center. Follow-up information will be included in the Army Medical Center's clinical investigation annual progress report for the particular study.

i. The referral service of the Army Medical Center (for example, Hematology-Oncology Service) is responsible for the following:

- (1) maintenance of all records pertaining to the clinical-investigation protocol,
- (2) periodic follow-up evaluation of the patients, as required by the protocol,
- (3) telephone consultation services, as needed, for the MTF physician, and
- (4) pharmacy consultation services, as needed, for the MTF physician.

j. If the MTF physician leaves the MTF (for example, transfer or separation), the physician must notify the Principal Investigator (PI) at the Army Medical Center of the planned departure in sufficient time to assure continuity of patient care. The new MTF physician should also take the actions described above. The PI at the Army Medical Center should correspond with the National Institutes of Health (NIH) or any research sponsor and remove the name of the departing MTF physician from the Form FDA 1572 as one of the subinvestigators and add the name of the new MTF physician. The PI must also notify Commander, U.S. Army Medical Department Center & School, Clinical Investigation Regulatory Office, ATTN: MCCS-GCI, 1608 Stanley Road, Fort Sam

Houston, TX 78234-6125 of the MTF physician removal and of the addition of the new MTF physician.

k. If the patient moves away from the care of the MTF, the MTF physician will notify the PI at the Army Medical Center, so that a determination can be made whether to extend the study to the patient's receiving MTF or to terminate the patient's enrollment in the protocol. This must be done with sufficient time to ensure appropriate patient care.

l. For NIH sponsored INDs, the Army Medical Center pharmacy will prepare and forward NIH Form 2564 (Investigational Agent Accountability Record) to the MTF for documenting the mailing of the investigational new drug from the Army Medical Center to the supported MTF. The MTF pharmacy will use this form for drug accountability. The MTF pharmacy will send a photocopy of the completed form back to the Army Medical Center when reordering or returning medications. An inventory form provided by the sponsor of the study may be used as an alternate to NIH Form 2564.

m. Records of an investigator's participation in the research protocol must be retained in accordance with the procedures identified in paragraphs 5-4 and 5-7.

n. For questions regarding the proper use of NIH Form 2564, consult the hematology/oncology pharmacist at the referring Army Medical Center.

## Army Medical Center Letterhead

Office Symbol

Date

MEMORANDUM FOR Commander, USAMEDDAC XYZ, ATTN: Rank/Name of  
Referring Physician, Address, City, State, Zip

SUBJECT: Instructions for Continuation of Patient \_\_\_\_ on Investigational New Drug  
Protocol

1. Our patient \_\_\_\_ (SSN \_\_\_\_\_) has a diagnosis of  
\_\_\_\_\_.

The patient was placed on the protocol entitled \_\_\_\_\_, a copy of which is attached.  
The patient was placed on investigational new drug \_\_\_\_\_ and an outline of the  
treatment schedule is attached. This investigational new drug protocol has been  
reviewed by this Army Medical Center's Clinical Investigation Committee on  
\_\_\_\_\_(date).

2. This review procedure fulfills the Food and Drug Administration (FDA) requirements  
for institutional review. If the patient enrolled in an investigational new drug protocol is  
returned to an MTF that has functioning scientific and ethical review committees, the  
protocol will require review and approval at the gaining MTF. Because of the  
investigational nature of this treatment, we remind you that FDA regulations require that  
Form FDA 1572, listing you as a subinvestigator, must be on file at the Drug Liaison  
and Distribution Section of the Division of Cancer Treatment of the National Cancer  
Institute, National Institutes of Health. Copies of these forms are enclosed for your  
convenience. Please fill them out and sign these forms as indicated. Return the forms  
to the undersigned. You must notify your Deputy Commander for Clinical Services and  
Chief of Service of this patient's investigational new drug treatment.

3. Coordinate with your Chief, Pharmacy Service concerning the dispensing and  
accountability requirements for the investigational new drug(s). Also, if your hospital  
has a Clinical Investigation Department, inform the Chief of Clinical Investigation of the  
arrival of the patient and the protocol. Your Pharmacy Service will receive instructions  
with the initial drug supply on the proper procedures for obtaining additional drug  
supplies from this Army Medical Center if they are needed.

4. It is essential that we communicate regarding the status of this patient, especially if  
there is a change in the patient's condition. To provide a mechanism for regular  
exchange of information, protocol flow sheets are provided. Upon completion of the  
flow sheet, send us the original in the enclosed envelopes, and maintain a copy in the  
patient's medical record. In addition, in the event you can no longer act as a

subinvestigator (for example, due to job change or transfer) you must notify the principal investigator with sufficient time to ensure appropriate patient care.

**Figure B-1. Example Memorandum for Transfer of Patients Enrolled in Treatment Protocols**

## OFFICE SYMBOL

SUBJECT: Instructions for Continuation of Patient \_\_\_\_ on Investigational New Drug Protocol

5. If you need further information, do not hesitate to contact us at DSN \_\_\_\_\_ or commercial \_\_\_\_\_. Thank you very much for your cooperation in the care of this patient.

/s/

- |   |  |
|---|--|
| 7 Encls   | Army Medical Center Referral Physician |
| 1. Treatment Protocol /                             | Chief, Oncology Section                |
| Outline   | Hematology-Oncology Service            |
| 2. Signed Consent                                   |  |
| (Copy of Original)                                  |  |
| 3. Flow Sheet (4 copies)                            |  |
| 4. Blank Flow Sheet (4 copies)                      |  |
| 5. Self-Addressed Envelope (4)                      |  |
| 6. Form FDA 1572                                    |  |
| 7. Drug-Information Summary/Investigators' Brochure |  |

CF: Medical Monitor  
Clinical Investigation Regulatory Office

Figure B-1. Example Memorandum for Transfer of Patients Enrolled in Treatment

## Protocols (continued)

## Appendix C Management Control Evaluation Checklist

### C-1. Function

The function covered by this checklist is the administration of the use of investigational new drugs and devices and the use of Schedule I controlled substances.

### C-2. Purpose

The purpose of this checklist is to assist assessable unit managers and Management Control Administrators in evaluating the key management controls as required by AR 11-2. It is not intended to cover all controls.

### C-3. Instructions

Answers must be based on the actual testing of key management controls (for example, document analysis, direct observation, sampling, simulation, auditing, other). Answers that indicate deficiencies must be explained and corrective action indicated in supporting documentation.

### C-4. Test questions

- a. Is AR 40-7 readily available for reference?
- b. Are investigators fully qualified as experts in the clinical study of investigational drugs or devices?
- c. Is the investigator's brochure (drug or device information) available?
- d. Are annual progress reports required by the sponsor and continuing review reports required by the IRB of record submitted in a timely manner?
- e. Are research protocols complete with background, hypothesis, objectives, military significance and methodology?
- f. Are literature references cited to support the research protocol?

g. Are human use protocols written in ICH format and do they include a copy of informed consent, case report forms and study specific procedures?

h. Do animal use protocols include animal use approval, justification for animal/species use, description of animal facilities, and evidence of compliance?

i. Is there evidence that the sponsor has provided clinical monitoring of the investigational new drug or device research protocol in accordance with 21 CFR 312 or 21 CFR 812.46, respectively, and the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6)?

j. Are the requirements for the protection of human participants identified in 21 CFR 50, 32 CFR 219 and AR 70-25 being followed?

k. Does the hospital or research facility have appropriate standing operating procedures for the conduct of clinical trials? At a minimum, procedures should be available for

- (1) Scientific review of research protocols.
- (2) Local human use review of research protocols.
- (3) Training and education of research staff in Good Clinical Practice (GCP).
- (4) Control and accountability of investigational products.
- (5) Maintenance of regulatory files.
- (6) Laboratory procedures (appropriate certification).
- (7) Study specific procedures.
- (8) Adverse event reporting.
- (9) Periodic reporting and final reports.
- (10) Informed consent process.

(11) Participant recruitment.

(12) Participant record maintenance.

l. Are procedures in place for emergency use of investigational products?

m. Are financial contracts with commercial sponsors signed?

n. Are procedures in place for participation in cancer cooperative group protocols?

o. Are procedures in place to ensure that participation in research does not conflict with 10 U.S.C 980?

p. Are final reports submitted at the conclusion of research activities?

q. For activities that use Schedule I controlled substances, are procedures in place to ensure the following:

(1) Has DEA Form 225 been completed?

(2) Is the Certificate of Registration available?

(3) Are the controlled substances correctly stored?

(4) Are security measures evident?

(5) Are dispensing records maintained correctly?

(6) Do only appropriate personnel have access?

(7) Can only authorized investigator(s) prescribe the controlled substance(s)?

(8) Do written records provide an audit trail of receipt, disposal, inventory and distribution?

#### C-5. Supersession

No prior version of this checklist has been published. This is the initial printing of a management control checklist for this regulation.

#### C-6. Comments

Help to make this a better tool for evaluating management controls. Submit comments to: Commander, United States Army Medical Research and Materials Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, MD 21702-5012.

## Appendix D Medical Devices

### D-1. Basic principles

The purpose of this appendix is to provide general information on the FDA regulation of medical devices. In addition, this appendix will provide references to additional sources of information. Medical devices range from simple tongue depressors and bedpans to laser surgical devices and complex programmable pacemakers with micro-chip technology. Medical devices also include *in vitro* diagnostic products, such as general purpose lab equipment, test kits that may include monoclonal antibody technology and reagents. In addition, certain electronic radiation emitting products with medical applications and claims meet the definition of a medical device. Section 201(h) of the Federal Food Drug and Cosmetic Act, 21 USC 301(codified at 21 USC 321(h)), states that the term "device" means the following:

"an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component part, or accessory which is:

(1) recognized in the official National Formulary, or the United States

Pharmacopoeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

## D-2. Device Advice Webpage

The Device Advice Webpage located at <http://www.fda.gov/cdrh/index.html> provides general information regarding the regulation of medical devices. This webpage is designed in a question and answer format to help users find information in an efficient manner. This resource is also hyperlinked to more specific guidance documents and regulations to allow users to easily access detailed information regarding a given topic. Topics discussed within the Device Advice Webpage include device classes, how to obtain market clearance, premarket notifications [510(k)], premarket approval, investigational device exemption, significant and nonsignificant risk device studies, good manufacturing practices and quality systems, and medical device reporting.

## D-3. Premarket Approval and Manual

Information regarding the content, formatting and procedures for Premarket Approvals (PMAs) can be found in the PMA Manual. Chapter 3 of the PMA Manual covers information necessary to complete a PMA application for submission to FDA. The PMA Manual can be found at D-Website: <http://www.fda.gov/cdrh/manual/pmamanul.pdf>

## D-4. Premarket Notification Manual

Information regarding the content, formatting and procedures for a Premarket Notification [510(k)] can be found in the Premarket Notification [510(k)] Manual. Chapter 3 of the 510(k) Manual covers information necessary to complete a 510(k) for submission to FDA. The 510(k) Manual can be found at D-Website: <http://www.fda.gov/cdrh/manual/510kp1.html>

## D-5. Investigational Device Exemption

Guidance on the conduct of device clinical trials can be found in the Investigational Device Exemption (IDE) Manual available at <http://www.fda.gov/cdrh/manual/idemanul.html>.

The IDE manual includes an overview of the provisions of the IDE regulation 21 CFR 812. The manual also provides suggested formats for an IDE submission, IDE application administrative checklist, and an IDE application cover letter.

#### D-6. Guidance on IDE Policies and Procedures

The document "Guidance on IDE Policies and Procedures" provides guidance that represents the FDA's current guidance on IDE Policies and Procedures. It includes guidance regarding changes in device regulation as a result of the Food and Drug Administration Modernization Act (the Modernization Act). The Modernization Act, enacted Nov. 21, 1997, amended the Federal Food, Drug, and Cosmetic Act (21 USC 301) relating to the regulation of food, drugs, devices and biological products.

"Guidance on IDE Policies and Procedures" is available at <http://www.fda.gov/cdrh/ode/idepolicy.html>.

#### D-7. IDE Regulation - 21 CFR Part 812

A full text version of 21 CFR 812 is available at [http://www.access.gpo.gov/nara/cfr/waisidx\\_00/21cfr812\\_00.html](http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr812_00.html).

#### D-8. Significant and nonsignificant risk investigations

IRBs are required to make a determination of risk for devices studied in clinical trials.

The FDA includes in their 1998 Update to Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators examples of nonsignificant risk (NSR)/significant risk (SR) devices to assist sponsors and IRBs in making NSR/SR

determinations. The lists include many commonly used medical devices and are available at <http://www.fda.gov/oc/ohrt/irbs/devices.html#risk>. Inclusion of a device in the NSR category should not be viewed as a conclusive determination, because the proposed use of a device in a study is the ultimate determinant of the potential risk to participants. It is unlikely that a device included in the SR category could be deemed NSR due to the inherent risks associated with most such devices.

#### D-9. Regulating *In Vitro* Diagnostic Device Studies

The FDA Guidance Document on regulating *in vitro* diagnostic device (IVD) studies is located at Website: <http://www.fda.gov/cdrh/comp/ivdreg.html>. The guidance explains how the Office of Compliance, Division of Bioresearch Monitoring, in conjunction with the Office of Device Evaluation (ODE), interprets and enforces the statute and regulations for investigational studies that involve the use of IVD's. Of particular concern for medical care and research is the requirement to file an IDE if the IVD is to be used for the purpose of diagnosing a disease. The IVD shall be labeled with the statement: "Caution-Investigational Use. Limited by Federal (or United States) law to investigational use." If the IVD is not to be used for medical diagnosis, the IVD label and all laboratory reports from use of the IVD must be clearly marked with the phrase, "For research purposes only."

## Glossary

### Section I

#### Abbreviations

AMEDD Center & School

U.S. Army Medical Department Center & School

AR

Army Regulation

BLA

Biologics License Application

CFR

Code of Federal Regulations

CIRO

Clinical Investigation Regulatory Office

DA

Department of the Army

DEA

Drug Enforcement Administration

DOD

Department of Defense

DTF

Dental Treatment Facility

FDA

Food and Drug Administration

FR

Federal Register

GCP

Good Clinical Practice

GLP

Good Laboratory Practice

HSRRB

Human Subjects Research Review Board

HUC

Human Use Committee (also HURC)

HURC

Human Use Review Committee (also HUC)

ICH

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IDE

Investigational Device Exemption

IND

Investigational New Drug application

IRB

Institutional Review Board

IVD

*In Vitro* Diagnostic Device(s)

MEDCEN

U.S. Army Medical Center

MEDCOM

U.S. Army Medical Command

MEDDAC

U.S. Army Medical Department Activity

MTF

Military Treatment Facility

NCI

National Cancer Institute

NBAC

National Bioethics Advisory Commission

NDA

New Drug Application

NIH

National Institutes of Health

NSR

Nonsignificant risk

ODE

Office of Device Evaluation (of the Food and Drug Administration)

PI

Principal Investigator

PMA

Premarket Approval Application

RCQ

Office of Regulatory Compliance and Quality

RDT&E

Research, Development, Test, and Evaluation

SAE

Serious Adverse Event

SR

Significant Risk

USAMRMC

United States Army Medical Research and Materiel Command

USC

United States Code

Section II

Terms

Adverse events

For the purpose of defining adverse events, this regulation follows the definitions provided in the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6)

and ICH Guideline for Clinical Safety Data Management (E2A) as it applies to

investigational new drugs and 21 CFR 812.3 as it applies to investigational devices. For

purposes of this regulation, the term “patient” is used to apply to all research participants. The definitions are as follows:

(1) Terms related to an investigational new drug.

(a) Adverse event. An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

(b) Serious adverse event. Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

(c) Unexpected adverse drug reaction. An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator’s Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

(2) Terms related to an investigational device.

(a) Unanticipated adverse device effect. An unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the

investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

#### Approving authority

A military or civilian member of an organizational element of a DA component who has been delegated authority to approve the use of human subjects in research. Per AR 70-25, the approving authority for all greater than minimal risk RDT&E research conducted by DA is The Army Surgeon General. The Surgeon General is also the approving authority for no greater than minimal risk research involving children.

#### Clinical investigation

An organized inquiry into health problems for all conditions that are of concern in providing healthcare to beneficiaries of the military healthcare system, including active duty personnel, dependents, and retired personnel. The clinical investigation program is described in AR 40-38.

#### DA sponsored IND

An IND application that identifies The Army Surgeon General or his or her designee as the sponsor of the application.

Device (as defined in 21 USC 321, Federal Food, Drug, and Cosmetic Act)

“(h) The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is -

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.”

Drug (as defined in 21 USC 321, Federal Food, Drug, and Cosmetic Act)

“(g)(1) The term "drug" means

(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and

(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

(C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and

(D) articles intended for use as a component of any article specified in clause (A), (B),

or (C). A food or dietary supplement for which a claim, subject to sections 403(r)(1)(B) and 403(r)(3) of this title or sections 403(r)(1)(B) and 403(r)(5)(D) of this title, is made in accordance with the requirements of section 403(r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement."

Human participant (from the National Bioethics Advisory Commission (NBAC) report of 30 April 2001 entitled, "Ethical and Policy Issues in Research Involving Human Participants)

Human participants are human beings who meet one of the following criteria:

- a. They are exposed to manipulations or interventions by investigators,
- b. They are exposed to interactions (e.g., surveys) by investigators,
- c. They provide data about themselves, or
- d. Identifiable data about them are collected or analyzed.

Excluded from this definition are deceased individuals, embryos, fetuses, the analysis of non-identifiable data from human beings, and information revealed about others.

Human subject (as defined in 32 CFR 219)

A living individual about whom an investigator conducting research obtained data through intervention or interaction with the individual, or identifiable private information. Intervention includes both physical procedures and manipulations of the subject or the

subject's environment for research purposes.

a. The term does not include military or civilian personnel who are qualified to test by assignment to duties that call specifically for such qualifications, such as test pilots and test engineers.

b. A minor (child) is a person who has not attained the legal age for consent to treatments or procedures involved in research under the applicable laws of the jurisdiction in which the research will be conducted.

c. Human subjects may be thought of as direct objects when the research is to determine the effects of a new system on humans (for example, the effect of a vaccine on immunogenicity) or as indirect objects when a test is conducted to determine how humans affect the ultimate performance of a system (doctrine concepts; training programs).

d. Per the NBAC report of 30 April 2001, use of the term human participant is recommended in lieu of the term human subject. This regulation (AR 40-7) therefore uses the term human participant to the extent possible. The term human subject is used in situations that refer to specific regulatory documents. These documents may change in the next few years to reflect the term human participant over human subject.

Human Subjects Research Review Board (as defined in OTSG Regulation 15-2)

The principal body of the Office of The Surgeon General for the assessment of practices and procedures by which DA employs human subjects in research, development, testing, and evaluation activities including clinical investigation activities.

Human Use Committee (also known as Human Use Review Committee) (as defined in AR 70-25)

A committee or board established to provide initial and continuing review of research involving the use of human subjects. A HUC is fundamentally similar to an IRB (21 CFR 56) but has somewhat different authority as compared to an IRB. Within DOD, authority to approve the use of human subjects in research is vested in commanders.

Commanders act on the recommendation of validly constituted HUCs. Outside DOD, IRBs tend to be vested with this authority.

Investigational device exemption (as defined in 21 CFR 812)

A device, including a transitional device, that is the object of an investigation. A transitional device means a device subject to section 520(1) of the Food, Drug and Cosmetic Act, that is, a device that FDA considered to be a new drug or an antibiotic drug before May 28, 1976.

Institutional Review Board (IRB) (as defined in 21 CFR 56.102)

IRB means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase institutional review committee in section 520(g) of the Food, Drug and Cosmetic Act.

**Investigational new drug (as defined in 21 CFR 312)**

A new drug or biological drug used in a clinical investigation. The term also includes a biological product that is used *in vitro* for diagnostic purposes. The terms “investigational new drug” and “investigational drug” are deemed to be synonymous. The term investigational new drug as defined in 21 CFR 312.3 means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used *in vitro* for diagnostic purposes.

**Investigator (as defined in 21 CFR 312)**

An individual who actually conducts a clinical investigation; that is, under whose immediate direction the drug is administered or dispensed to a subject. In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. “Subinvestigator” includes any other individual member of that team.

**Investigator-sponsor (defined as sponsor investigator in 21 CFR 312)**

An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to investigator-sponsor under this definition include both those applicable to an investigator and a sponsor.

**IRB of Record (from FDA Information Sheets, Guidance for Institutional Review Boards)**

and Clinical Investigators – “Cooperative Research” and “Non-Local IRB Review”)

The IRB designated with primary responsibility for the oversight and conduct of a particular research protocol to include review of adverse events, protocol amendments, and continuing review of research activities.

NCI cooperative group

A cooperative group of investigators in the field of cancer therapy who are registered with and sponsored by the NCI, NIH, Bethesda, Maryland, which provides financial support to the group.

New Drug (as defined in 21 USC 355, Federal Food, Drug, and Cosmetic Act)

“(p) The term “new drug” means -

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a “new drug” if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of

investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.”

#### Non-DA sponsored IND

An IND application sponsored by an agency or individual not affiliated with the DA. This definition does not include DA employees who are sponsor-investigators.

#### Phases of an investigation for investigational drugs (from 21 CFR 312)

a. Phase I includes the initial introduction of an investigational new drug into humans. Phase I studies are typically closely monitored and may be conducted in patients or normal volunteers. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans and the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase I, sufficient information about the drug’s pharmacological effects should be obtained to permit the design of well controlled, scientifically valid, Phase II studies. The total number of subjects and patients included in Phase I studies varies with the drug, but is generally in the range of 20 to 80. Phase I studies also include studies of drug metabolism, structure activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

b. Phase II includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the

disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase II studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

c. Phase III studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about efficacy and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase III studies usually include from several hundred to several thousand subjects.

d. Phase IV. Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (Phase IV) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedule of administration than were used in Phase II studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time. For approved NDAs for which The Army Surgeon General is the sponsor, the conduct of phase IV will be the responsibility of the Office of Regulatory Compliance and Quality, USAMRMC.

Protocol (as defined in the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6))

A document that describes the objective(s), design, methodology, statistical

considerations, and organization of a clinical trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol-referenced documents. The website for the Office of Regulatory Compliance and Quality contains a template for IND protocols.

#### Radiation control committee (as defined in AR 70-25)

A committee appointed by the commander to ensure that individual users of radioactive materials within the medical facility and each radionuclide used will be approved and controlled. The approval and control must be in accordance with the requirements specified in the conditions of the Nuclear Regulatory Commission license, the DA radioactive material authorization, and appropriate Federal directives.

#### Research (as defined in 32 CFR 219)

A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. The term does not include individual or group training of military personnel such as combat readiness, effectiveness, proficiency, or fitness exercises (DOD Directive 3216.2.)

#### Research, development, test, and evaluation (as defined in AR 70-25)

The categories of research and development included in Program 6, Research and Development, and operational systems development contained in the Five-Year Defense Program.

### Schedule I controlled drug substance

Any drug or substance by whatever official name, common or usual name, chemical name, or brand name listed in 21 CFR 1308.11; for example. DEA Schedule I controlled substances are drugs having a high abuse potential and no accepted medical use (e.g., heroin, marijuana, LSD).

### Sponsor (from 21 CFR 312)

A person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is an investigator-sponsor. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not an investigator-sponsor, and the employees are investigators.

### Subinvestigator (as defined in the ICH Guideline for Good Clinical Practice: Consolidated Guideline (E6))

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g. associates, residents, research fellows). See Investigator.

### Supplier (of a drug, vaccine, or biological product)

An activity that serves as a provider of drugs, vaccines, and biologicals used in an Army MTF. These providers include commercial pharmaceutical distributors, as well as elements of the military medical logistics system, such as installation medical supply accounts, U. S. Army medical materiel centers, Defense Supply Center, Philadelphia, and medical depots.

Treatment IND (as defined in 21 CFR 312)

The FDA may permit the use of an investigational drug to be used for treatment use under a treatment protocol or treatment IND under the following conditions: if the drug is intended to treat a serious or immediately life-threatening disease; there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population; the drug is under investigation in a controlled clinical trial under an IND in effect for the trial or all clinical trials have been completed; and the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

### Section III

Special abbreviations and terms

This section contains no entries.

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